

allows it to be bound to the gold antenna but also has a prominent vibrational mode that is both Raman-scattering and IR-absorption active.

By multiplying the enhancement factor from the focusing and anti-Stokes Raman scattering, it is estimated that a 10^{10} -fold efficiency enhancement can be achieved, with a potential enhancement factor of up to 10^{13} . The final result is the pronounced improvement in detection sensitivity demonstrated by Chen *et al.* in the detection of a mid-IR signal of less than a microwatt.

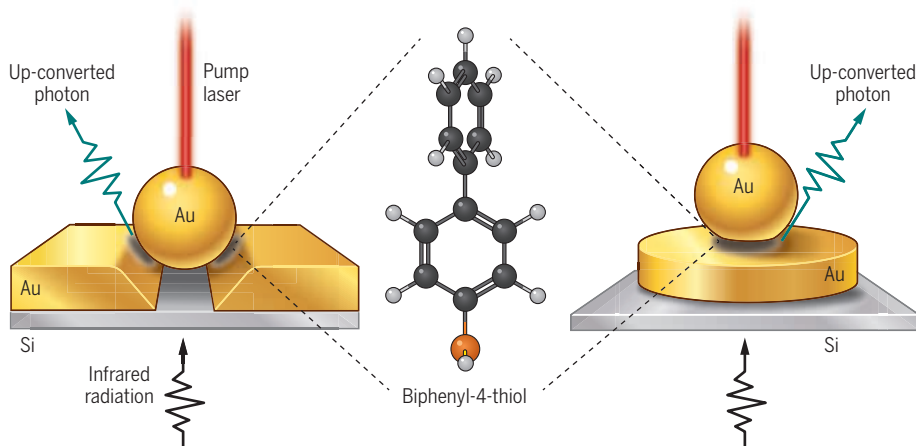
Although both studies showed outstanding sensitivity, far greater sensitivity is possible. For instance, silver may provide a greater enhancement than gold (3, 4). Better antenna design can also bring further improvement. For example, an an-

entanglement or quantum state manipulation, with potential applications in quantum computing.

Chen *et al.* and Xomalis *et al.* demonstrate a sensitive IR detection technique built upon decades of research in surface-enhanced Raman scattering (SERS), surface-enhanced IR absorption spectroscopy (SEIRA), and cavity quantum optomechanics. Substantially greater sensitivity is expected from these platforms by material optimization and antenna design. There is still the challenge of extending the platform to other IR wavelengths by finding molecules with simultaneous Raman and IR active vibrations in different energy ranges of interest. Perhaps more important than their use in room-temperature IR detection, these studies introduce a

Two antenna designs for detecting infrared light

Both designs by Chen *et al.* and Xomalis *et al.* include a mid-infrared (mid-IR) antenna and a near-IR antenna. Chen *et al.* used a golden nanoparticle inside a 100 nm wide slot on a gold film, whereas Xomalis *et al.* also used a golden nanoparticle, but drop-casted on a microscopic gold disk. Both groups put biphenyl-4-thiol molecules in the tiny gap between the gold nanoparticle and the gold underneath it.



tenna with higher directivity will increase collection efficiency, such as those used in single-photon quantum light sources (5, 6). With these modifications, it is expected that the same scheme could operate at the single-molecule level in the near term.

Once the single-molecule level is achieved, new quantum physics applications become possible by using the combined Raman scattering and IR absorption platform. Indeed, researchers have been advancing the field of quantum cavity optomechanics for years (7, 8). The ability of a molecule's electronic state to coherently interact with its vibrational states through IR light offers a previously unexplored way to manipulate the quantum state of the molecule. It is also possible to couple between multiple molecules on a single chip using waveguides, which will allow for

new quantum playground where unprecedented coherent manipulation and read-out are possible. Based on past works on SERS and SEIRA, it is foreseeable that this will soon scale down to the single-molecule level, thereby enabling new quantum physics and information applications. ■

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VIEWPOINT: COVID-19

Dissecting the early COVID-19 cases in Wuhan

Elucidating the origin of the pandemic requires understanding of the Wuhan outbreak

By Michael Worobey

Some key questions lie at the heart of investigations into the origin of the COVID-19 pandemic, including what is known about the earliest COVID-19 cases in Wuhan, China, and what can be learned from them? Despite assertions to the contrary (1), it is now clear that live mammals susceptible to coronaviruses, including raccoon dogs (*Nyctereutes procyonoides*), were sold at Huanan Market and three other live-animal markets in Wuhan before the pandemic (2, 3). Severe acute respiratory syndrome-related coronaviruses (SARSr-CoVs) were found in raccoon dogs during the SARS outbreak, which was facilitated by animal-to-human contact in live-animal markets in China. However, because of the early public health focus on Huanan Market, it remains unclear whether the apparent preponderance of hospitalized COVID-19 cases associated with this market was truly reflective of the initial outbreak. Answering these questions requires resolving several crucial events that took place in December 2019 and early January 2020.

On 30 December 2019, the Wuhan Municipal Health Commission (WHC) issued two emergency notices for internal circulation to local hospitals alerting them to patients with unexplained pneumonia—several of whom worked at Huanan Market—and laying out a treatment and response plan (see fig. S1). The first official public report was WHC's announcement the next day that they had carried out case searches and retrospective investigations related to Huanan Market and found 27 patients. Forty-one of the first known patients formed the basis of an influential study that reported that 66%—i.e., not all early cases—had a link to Huanan Market

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(4). They had been transferred between 29 December and 2 January from other hospitals to Jinyintan Hospital, Wuhan's premier infectious disease center. Notably, individuals were enrolled according to clinical presentation, not epidemiologic information, such as connections to Huanan Market (4).

China's Viral Pneumonia of Unknown Etiology (VPUE) mechanism was set up in the wake of SARS to be an early warning reporting system for detecting unknown viral diseases and is overseen by the China Center for Disease Control and Prevention (CCDC) (5). PUE cases are supposed to be rapidly reported by clinicians to the national notifiable disease reporting system through an internet-based platform. Evidently, that did not happen in Wuhan in December. The system appears to have been in active use only from 3 January. Although it favored cases having a connection to Huanan Market (6–8), the VPUE mechanism could not have improperly inflated the proportion of Huanan Market-linked cases in December (1). Moreover, reporting began only after the 41 patients were transferred from other hospitals to Jinyintan Hospital. Nevertheless, it is possible that a disproportionate number of cases linked to Huanan Market were transferred to Jinyintan Hospital because of public health officials' early focus there.

There is, however, a way to step back to a period before any such bias could have crept in, by considering what happened in the hospitals that first pieced together that a new viral outbreak was underway. Although not mentioned by name in scientific publications (9), media reports reveal that Hubei Provincial Hospital of Integrated Chinese and Western Medicine (HPHICWM) was the first hospital to alert district, municipal, and provincial public health authorities about the mysterious pneumonia cases (see fig. S1). Zhang Jixian, director of respiratory and critical care medicine, noticed on 27 December that an elderly couple had large “ground glass” opacities in computed tomography (CT) images of their lungs, distinct from those she had seen in other cases of viral pneumonia. Zhang insisted that the couple's son, who was not a patient and had no symptoms, undergo a CT scan, and the same unusual lesions were observed. The husband and wife evidently are “cluster 1” in the World Health Organization (WHO)–China report (1): They are the earliest known case cluster and the only cluster admitted by 26 December. They had no known connection to Huanan Market.

Another patient with similar CT imaging, a worker at Huanan Market, was admitted on 27 December. Zhang, concerned about a new, probably infectious viral disease, reported the four cases to hospital officials,

who alerted the Jiangnan District CDC that same day. Over 28 and 29 December, three more patients, all of whom worked at Huanan Market, were admitted and recognized to have the same unknown respiratory disease. A vice president of HPHICWM, Xia Wenguang, brought together 10 experts from the hospital, including Zhang, for an emergency meeting on 29 December, and they concluded that the situation was extraordinary. Upon learning of similar patients, also linked to Huanan Market, at Tongji and Union (Xiehe) Hospitals, Xia alerted the Wuhan and Hubei CDCs on 29 December.

A notably similar situation unfolded at Wuhan Central Hospital. On 18 December, Ai Fen, director of the emergency department, encountered her first unexplained pneumonia patient, a 65-year-old man who had become ill on either 13 or 15 December. Unbeknownst to Ai at the time, the patient was a deliveryman at Huanan Market. A CT scan revealed infection in both lungs, and he did not respond to antibiotics or anti-influenza drugs. On 24 December, a bronchoalveolar lavage specimen collected from him was sent to Vision Medicals, a metagenomics sequencing company. They identified a new SARS-CoV on 26 December and relayed the finding by telephone to the hospital on 27 December. By 28 December, Wuhan Central Hospital had identified seven cases, of which four turned out to be linked to Huanan Market. Notably, these seven cases, like those at HPHICWM, were ascertained before epidemiologic investigations concerning Huanan Market commenced on 29 December.

At Zhongnan Hospital in the Wuchang District of Wuhan, 15 km away from Huanan Market and on the opposite bank of the Yangtze River, Vice President Yuan Yufeng asked units on 31 December to search for unexplained pneumonia cases, and the Respiratory Medicine Department reported two. The first lived in Wuchang District but worked at Huanan Market (in Jiangnan District). The second did not work at Huanan Market but had friends who did and who had visited his home. On 3 January, three more cases were identified—a family cluster unlinked to Huanan Market. Clearly, hospitals in the first weeks of the outbreak were identifying cases both with and without a known connection to Huanan Market. And Wuhan hospitals were not swamped with unexplained pneumonia cases at the end of December—that would come later.

Thus, 10 of these hospitals' 19 earliest COVID-19 cases were linked to Huanan Market (~53%), comparable both to Jinyintan's 66% (of 41 cases) (4) and to the WHO–China report's 33% of 168 retrospectively identified cases within Wuhan across December 2019 (1). Regarding cases at the

Wuhan Central Hospital and HPHICWM, patients with a history of exposure at Huanan Market could not have been “cherry picked” before anyone had identified the market as an epidemiologic risk factor. Hence, there was a genuine preponderance of early COVID-19 cases associated with Huanan Market.

How can this knowledge inform our understanding of the pandemic? If Huanan Market was the source, why were “only” one- to two-thirds of early cases linked to the market? Perhaps a better question is why would one expect all cases ascertained weeks into the outbreak to be confined to one market? Given the high transmissibility of SARS-CoV-2 and the high rate of asymptomatic spread, many symptomatic cases would inevitably soon lack a direct link to the location of the pandemic's origin. And some cases counted as “unlinked” may have been only one or two transmissions away, as exemplified by the second patient identified at Zhongnan Hospital. That so many of the >100 COVID-19 cases from December (1) with no epidemiologic link to Huanan Market nonetheless lived in its direct vicinity is notable (see the figure) and provides compelling evidence that community transmission started at the market.

Additionally, the earliest known cases should not necessarily be expected to be the first infected or linked to Huanan Market: They probably postdated the outbreak's index case by a considerable period (10). Moreover, only ~7% of SARS-CoV-2 infections lead to hospitalization (11); most fly under the radar. Similarly, it is entirely expected that early, ascertained cases from a seafood market would be workers who were not necessarily directly associated with wildlife sales once the outbreak began spreading from human to human. The index case was most likely one of the ~93% who never required hospitalization and indeed could have been any of hundreds of workers who had even brief contact with infected live mammals.

Crucially, however, the now famous “earliest” COVID-19 case (1), a 41-year-old male accountant, who lived 30 km south of Huanan Market and had no connection to it—illness onset reported as 8 December—may have become ill with COVID-19 considerably later (12). When interviewed, he reported that his COVID-19 symptoms started with a fever on 16 December. This is corroborated by hospital records and a scientific paper that reports his COVID-19 onset date as 16 December and date of hospitalization as 22 December (see fig. S1). This suggests that he may have been infected through community transmission after the virus had begun spreading from Huanan Market. He believed that he may have been infected in a hospital or on the subway during his commute; he had also traveled north of Huanan

Market shortly before his symptoms began (12). If his symptoms indeed began on 16 December, then it postdated multiple cases in workers at Huanan Market, making a female seafood vendor there the earliest known case, with illness onset 10 December (see fig. S1). Notably, she reported knowledge of several possible COVID-19 cases in clinics and hospitals that were near Huanan Market from 11 December, and Huanan Market patients were hospitalized at Union Hospital as early as 10 December (see fig. S1).

Although a widely cited report (7) credits the VPUE mechanism with uncovering the pandemic, it was HPHICWM that identified both the outbreak and the Huanan Market connection and passed on these fully formed discoveries to district, municipal, and provincial public health officials by 29 December (9). National officials reportedly did not learn about the outbreak until CCDC Director George Gao encountered online group chats about the WHC emergency notices on the evening of 30 December. Concerned that so many cases had not been reported to the VPUE system, he quickly notified the National Health Commission (13) (see fig. S1).

Therefore, the preponderance of early cases connected to Huanan Market could not have been an artifact of ascertainment bias introduced by case definitions in the VPUE system. Although mechanisms like China's VPUE system are potentially invaluable, they will fail without both widespread buy-in from health care providers and rapid data sharing from local to central authorities. Key problems with the VPUE system were known before the pandemic, including that most clinicians in China had little awareness of the VPUE system and were not reporting cases to it—for example, 0 of 335 PUE cases in one study from 2019 (5). China should be commended, however, for having such a system, which is lacking in most countries. The focus now should be on fixing the problems that COVID-19 has exposed and blanketing the globe with a highly functional PUE early warning system.

Samples from the earliest COVID-19 patients in Wuhan have been sequenced, and two distinct SARS-CoV-2 lineages, A and B, have been identified. Given that the elderly couple at HPHICWM was the WHO report's cluster 1, it follows that the husband, illness onset 26 December (1), must be the source

COVID-19 cases in Wuhan in December 2019

The map shows that most of the earliest cases of COVID-19 were in close proximity to Huanan Market, even if they were not directly connected with the market through working there or visiting. This suggests that transmission in the community around the market was occurring in December 2019. The map is based on a subset of data from 174 COVID-19 cases in and around Wuhan (1).



of the earliest lineage A sequence, Wuhan/IME-WH01/2019 (GenBank accession number MT291826) (see fig. S1), which he most likely got from his wife, who became ill 15 December. This raises the possibility that the Yangchahu Market that they visited may have been a site of a separate animal spillover. The recent discovery that there may be no true lineage A or B intermediates in humans (14) also raises the possibility of separate spillovers of both lineages. However, the earliest known lineage A genomes have close geographical connections to Huanan Market: one from a patient (age and gender not reported) who stayed in a hotel near Huanan Market in the days before illness onset in December (15) and the other from the 62-year-old husband in cluster 1 who visited Yangchahu Market, just a few blocks north of Huanan Market (1), and lived just to the south (see the figure). Therefore, if lineage A had a separate animal origin from lineage B, both most likely occurred at Huanan Market, and the association with Yangchahu Market, which does not appear to have sold live mammals, is likely due to community transmission starting in the neighborhoods surrounding Huanan Market.

With SARS, live-animal markets continued to sell infected animals for many months, allowing zoonotic spillover to be established as the origin and revealing multiple independent jumps from animals

into humans (3). Unfortunately, no live mammal collected at Huanan Market or any other live-animal market in Wuhan has been screened for SARS-CoV-2-related viruses (1), and Huanan Market was closed and disinfected on 1 January 2020. Nevertheless, that most early symptomatic cases were linked to Huanan Market—specifically to the western section (1) where raccoon dogs were caged (2)—provides strong evidence of a live-animal market origin of the pandemic.

This would explain the extraordinary preponderance of early COVID-19 cases at one of the handful of sites in Wuhan—population 11 million—that sell some of the same animals that brought us SARS. Although it may never be possible to recover related viruses from animals if they were not sampled at the time of emergence, conclusive evidence of a Huanan Market origin from infected wildlife may nonetheless be obtainable through analysis of spatial patterns of early cases and from additional genomic data, including SARS-CoV-2-positive samples from Huanan Market, as well as through integration of additional

epidemiologic data. Preventing future pandemics depends on this effort. ■

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SUPPLEMENTARY MATERIALS

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